REMARKS

Claims 3-5 and 11-14 are pending in the subject application. No claim has been added, canceled, or amended herein. Accordingly, claims 3-5 and 11-14 are still pending and under examination.

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 3-5 and 11-14 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable a method for preventing exaggerated restenosis in a diabetic subject by administering to said subject any sRAGE polypeptide other than murine sRAGE in vivo.

Specifically, the Examiner states, in relevant part, that the claims encompass the use of numerous sRAGEs, which have different amino acid sequences, and are derived from different organisms, to prevent exaggerated restenosis in a diabetic subject in vivo, and alleges that no information for the structural feature of sRAGE that contributes to preventing exaggerated restenosis has been provided.

In response, applicants respectfully traverse.

Claim 3, and dependent claims 4, 5 and 11-14, provide a method for preventing exaggerated restenosis in a diabetic subject at risk of developing exaggerated restenosis which comprises administering to the subject a therapeutically effective amount of soluble receptor for advanced glycation endproducts (sRAGE) so as to prevent exaggerated restenosis in the subject.

For a claim to be enabled, it is necessary that one skilled in the art at the time of filing could practice the claimed invention in view of the specification without undue experimentation. In the event some experimentation were required to practice the invention, which applicants do not concede, the need for such experimentation does not by itself constitute a lack of enablement. Rather, for that to happen, the experimentation must be undue.

Here, applicants have provided a representative number of embodiments of sRAGE to enable the pending claims. For example, applicants provide both DNA and amino acid sequences for murine, bovine and human RAGE, and note that RAGE sequences for other species are known (specification at pages 13-19). It is unnecessary for applicants to further provide discussion of structural features responsible for sRAGE function, so long as the meaning of sRAGE (i.e., the extracellular ligand-binding domain of the receptor) is clear (see, e.g., page 31, lines 8-9 of the specification).

In view of the above, applicants maintain that claims 3-5 and 11-14 are enabled.

The Examiner further rejected claims 3-5 and 11-14 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable a method for preventing exaggerated restenosis in a diabetic human subject by administering to said subject any sRAGE polypeptide in vivo.

Specifically, the Examiner states that even though sRAGE can prevent exaggerated restenosis in an animal model, the data from

the animal model allegedly cannot be extrapolated into success in preventing exaggerated restenosis in a human subject.

In response to the Examiner's rejection of claims 3-5 and 11-14, applicants respectfully traverse.

The claimed invention is discussed above.

Pages 28-34 of the subject application set forth results from experiments involving fatty Zucker rats (also known as obese Zucker rats). In these experiments, it was shown that the blockade of RAGE in fatty Zucker rats by the administration of sRAGE suppresses exaggerated neointimal expansion (specification at pages 33-34). This finding provides a means for preventing excessive restenosis in subjects with diabetes (specification at page 34).

In support of the Examiner's position, the Examiner cites Muller, et al., Reilly, et al. and Lafont, et al. as teaching that "successful application of restenosis treatments in small animal models is not predicative of success in other animals, particularly in humans" (Office Action at page 5).

Applicants maintain that the rat models discussed in Muller, et al., Reilly, et al. and Lafont, et al. differ fundamentally from the fatty Zucker rat used in experiments in this application.

In support of this position, applicants attach hereto as **Exhibit 1** a Declaration under 37 C.F.R. §1.132 of Ann Marie Schmidt, M.D., a co-inventor named in the subject application. In the Declaration, Dr. Schmidt establishes the following:

1. To her understanding, each of Muller, et al., Reilly, et al. and Lafont, et al. discusses the use of rat models for the study of restenosis. Also to her understanding, each of these references (i.e., Muller, et al. at page 428, Reilly, et al. at pages 143-144 and Lafont, et al. at page 52) indicates the disease-free arterial state of rat models as a disadvantage of such models in predicting human clinical outcome in treating restenosis. None of Muller, et al., Reilly, et al. and Lafont, et al. discusses the fatty Zucker rat model used in the subject application.

2. Fatty Zucker rats (i.e., those used for the experiments discussed in the subject application) are not healthy or normal rats. In support of this statement, she attaches to her Declaration as **Exhibit B** a copy of Park, et al. ("Neointimal Hyperplasia After Arterial Injury is Increased in a Rat Model of Non-Insulin-Dependent Diabetes Mellitus," Circulation 104:815-819 (2001)). At page 815, Park, et al. state that the fatty Zucker rat is "characterized by excessive body weight, insulin resistance, hyperinsulinemia, and mild hyperglycemia" and "is a well-established model of type II diabetes."

3. Moreover, the arteries of fatty Zucker rats are diseased, as are those of diabetic humans. The response of fatty Zucker rat arteries following carotid balloon injury parallels the results observed in diabetic human subjects following carotid balloon angioplasty. As described by Park, et al., when subjected to identical degrees of

> balloon injury, compared to lean Zucker rats (nondiabetic), neointimal area was increased >2-fold in the diabetic obese Zucker rats. In parallel, medial cell proliferation was also higher after injury in diabetic obese Zucker rats relative to nondiabetic lean Zucker rats.

In summary, applicants note that Muller, et al., Reilly, et al. and Lafont, et al. discuss rat models having disease-free arteries. Applicants also note that, in contrast, the fatty Zucker rat used in this application has diseased arties, as do diabetic humans. Indeed, it is a well-established model of type I diabetes.

The Examiner has asserted that the rat models discussed in the cited references are not predicative of human outcome regarding preventing exaggerated restenosis in diabetics. However, based on the severe discrepancy between the fatty Zucker rat and the rat models discussed in the cited references, the Examiner's assertion and supporting references are inapposite to the utility of the fatty Zucker rat in this regard.

Finally, applicants briefly note the comments made in the "Study Limitations" section on page 819 of Park, et al. There, Park, et al. state that the "relevance of restenoic animal models to human restenosis is unknown, and no single animal model has yet been shown to reliably predict restenosis in humans. In fact, it is unlikely that any one model will be entirely explanatory of the human response to injury."

Applicants understand the first sentence of this statement simply

as reflecting the authors' understanding of an absence of human clinical data establishing the predicative value of fatty Zucker, or other, rat models. Regarding the second sentence of this statement, applicants note that for an animal model to be useful, i.e. correlative with human outcome, it is not necessary that it be "entirely explanatory of the human response to injury."

In view of the above, applicants maintain that claims 3-5 and 11-14 are enabled and satisfy the requirements of 35 U.S.C. §112, first paragraph.

Summary

For the reasons set forth hereinabove, applicants maintain that the claims pending are in condition for allowance, and respectfully request allowance.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the $60.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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